Wyeth Pharmaceuticals

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2005D-0062: May 10, 2005 (70 FR 24606-24607)

Dear Sir/Madam:

Wyeth Pharmaceuticals is submitting the following comments on the FDA's draft guidance for industry entitled, "FDA's 'Drug Watch' for Emerging Drug Safety Information" (May 2005).

Wyeth is one of the largest research-based pharmaceutical and healthcare products companies and is a leading developer, manufacturer and marketer of prescription drugs, biopharmaceuticals, vaccines, and over the counter medications.

In general, Wyeth supports the fundamental concept of forming an expert drug safety advisory board to evaluate and advise on critical safety issues. Wyeth also supports, conceptually, the Agency's effort to increase the transparency of FDA-industry deliberations on drug safety to healthcare providers, patients and other stakeholders. We are concerned, however, that posting of preliminary information about safety issues that have not been fully evaluated or substantiated could lead to confusion and unnecessary alarm for patients and health care providers rather than conveying important and useful findings. Our comments and recommendations to address this concern are described below.

Potential Public Health Considerations

The public health consequences of posting preliminary, unconfirmed information do not appear to be considered as a factor in the decision making process (section III.B. of draft guidance). The guidance should consider how FDA can best inform and involve the medical community to ensure physicians are not surprised by patients' questions about posted information, and reduce the likelihood that patients will draw inappropriate conclusions resulting from miscomprehension of the significance of preliminary information – possibly resulting in treatment decisions that are not in their best interests. We recommend the posting should indicate, for

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example, whether or not any specific action is recommended on the part of patients or physicians.

Another concern is that posting information on a preliminary, unconfirmed safety issue could actually impede efforts to further evaluate the "emerging" issue. Spontaneous reporting systems may no longer be useful for this purpose because the publicity resulting from posting on FDA's web site could artificially inflate the reporting rate. In addition, concern resulting from the posting could also limit enrollment into prospective studies intended to evaluate the issue. Due to the potential for such unintended consequences, we believe it is essential for FDA to take these factors into account, in addition to evaluating the credibility of the emerging issue, when making decisions on posting emerging safety information.

Content of Posting

The draft guidance fails to consider inclusion of any balancing positive information about the drug (e.g., statement of approved indication(s) or benefits for physicians/patients to consider). The lack of balance could undermine treatment decisions for patients with serious medical conditions. We recommend that the posting should be balanced by including information on the approved uses and benefits of the drug (with links to the approved physicians labeling and patient information, if available) and when appropriate, information on potential risks if a patient elects to discontinue treatment based on a preliminary and unsubstantiated safety concern that FDA has identified. We further recommend that the posting should describe any uncertainties surrounding the emerging safety issue and any steps FDA is planning to take to evaluate it.

Possible Confusion Between Drug Watch and New Label Warnings

At least one of the categories of potential Drug Watch information identified in the draft guidance – "*information about significant emerging risks that FDA believes may be associated with a drug*" (lines 96-98) – appears to be information that would more properly be included in a drug's labeling, as the corresponding example given in the draft guidance illustrates (lines 100-101). The value of posting such information in this forum is highly questionable, particularly in light of the preliminary and qualified nature of the underlying information: "*By definition . . . the information posted on the Drug Watch is information about which FDA has made no final regulatory judgment.*" (See lines 136-137.)

In view of the preliminary nature of the information to be posted, we recommend that FDA specifically state if the information is not considered to be sufficient to warrant a change in the product's labeling. We further recommend that the Drug Watch web site include an explanation to viewers noting that posting of information about a product does not mean that the manufacturer is required to take any specific action related to the posted information.

Sponsor Participation

The draft guidance indicates FDA will notify the sponsor shortly before posting (lines 216-218), however, sponsors will not be provided an opportunity to have input into the decision or the verbiage to be used in the posting.

Sponsors should have a reasonable period of advance notification and an opportunity to participate in the posting process in view of the potentially significant impact on patient and physician behavior. This is also important due to the potential for posting inaccurate information that could confuse physicians and patients, and cause potentially irreparable damage to the product and to the sponsor if the "emerging" safety issue is subsequently determined to lack validity. In addition, sponsors need time to evaluate the potential necessity for updating the current product labeling in light of the information to be posted, and to prepare for responding to patient and physician inquiries.

Therefore, we recommend that a minimum of two weeks advance notice be provided, with opportunity to request an extension if additional time is needed to complete a preliminary evaluation and assess whether the information is credible. In addition, FDA should be willing to re-evaluate the initial decision to post information if the sponsor is able to show that the information is inaccurate or the scientific plausibility is dubious.

Access to Underlying Data

The draft guidance does not ensure that sponsors will have access to the data, report, and analysis along with the supporting rationale underlying a posting. While in many cases, the potential safety concern might be identified from reports submitted by the sponsor, any subsequent analysis or data searches performed by FDA would not be known to the sponsor. It is important for sponsors to have timely access to the underlying information and the opportunity to address any potential omissions or inaccurate information. We recommend that the guidance specifically indicate that the sponsor notification will identify the source of the information, and that a copy, including any special analyses performed by FDA, will be furnished if the sponsor does not already have the relevant information.

Decision-making Criteria

The criteria to be used for decisions on posting are not sufficiently defined. This is a critical omission in a process that by its own terms focuses on "emerging safety information" to be publicly posted on an FDA website "before [FDA] has fully determined its significance" (lines 64-65). Given the risk of premature and/or inaccurate posting of information that could lead to confusion among physicians and apprehension among patients, it is crucial to have clearly defined parameters

for the selection of information to be posted. The draft guidance states, for example, that before posting information FDA will conduct a preliminary analysis to determine that it is "sufficiently credible" to warrant public dissemination (lines 167-169). This standard lacks sufficient detail and rigor to provide adequate guidance for such an important decision. If the threshold is too low, the likelihood increases that preliminary information will be posted that cannot be substantiated, resulting in unnecessary confusion for patients and physicians, and potentially impacting appropriate product usage and enrollment in clinical trials for new indications. Hence, it is important to establish more specific criteria to guide these determinations, taking into account factors such as scientific plausibility and clinical trial experience, in addition to the potential public health consequences of posting preliminary information.

Decision-Making Structure

The draft guidance indicates that the Drug Safety Oversight Board (DSB) will manage the Drug Watch program and decide when information should be posted or removed from the web site (lines 173-178). However, the recently issued CDER procedure, MAPP 4151-3, describing the structure, roles and responsibilities of the Drug Safety Oversight Board, indicates decisions to post or remove information on Drug Watch will be made by a subcommittee consisting of the DSB chair and no more than 5 additional members. We question the rationale for delegating such important decisions to a small subcommittee of the DSB. If an emerging issue were based on preliminary information that requires further evaluation and verification, there would not appear to be a compelling reason to rush a posting in advance of full consideration by the DSB. We therefore recommend that decisions to post information on the Drug Watch web site should be a function of the full DSB. In the occasional situations when it might be appropriate to expedite the posting, and there is a clear basis for believing the information underlying the concern is credible, FDA should consider convening the full Board on an ad hoc basis rather than reviewing decisions of a subcommittee post hoc.

Lack of Mechanism for Sponsor Response

Once information about a sponsor's product has been posted, the draft guidance does not include a provision for the sponsor to appeal the decision or to propose alternative wording. A mechanism should be established for the sponsor to request Board review, and potentially modification or withdrawal of the posted information, based on compelling information showing that the posting was inaccurate, unclear, or lacked a credible basis.

Removal of Posted Information

The draft guidance states that FDA plans to regularly update the information on the Drug Watch page as new information becomes available (lines 207-208), including situations when FDA has determined that, despite the initial signal that led to the

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decision to post, it is ultimately concluded that there is no new safety concern (lines 211-212). We hope that thoughtful decision-making coupled with adoption of clearer criteria will minimize the potential for posting emerging safety information that is later determined to be unfounded. Nonetheless, recognizing the distinct possibility that this will occur, we recommend that the guidance specifically state that once such a determination is made the inaccurate information will be promptly removed from the web site. In addition, an explanation for the removal (e.g., upon further analysis/evaluation the original concern was determined to be unsubstantiated, etc.) should remain on the web site for a set period of time, with prominence comparable to that given to the issue when it was initially posted. There should also be a sunset provision for withdrawal of posted information if, after a substantial time period, no information can be produced to validate a theoretical concern.

Disclaimer Statement

The proposed disclaimer statement for emerging safety information (see lines 121 – 124, and footnote no. 5 on page 4 of the draft guidance) should specifically indicate if a causal relationship has not been established, and that the validity of the posted information is subject to verification.

We are submitting the enclosed comments in duplicate. Wyeth appreciates the opportunity to comment on the above-mentioned draft guidance, and trusts that the Agency will take these comments into consideration when finalizing the Drug Watch guidance document.

Sincerely,

Roy Baranello

Roy J. Baranello, Jr.
Assistant Vice President,
Regulatory Policy & Operations